SYPHILIS, TUBERCULOSIS, AND SICKLE-CELL ANÆMIA: REPORT OF A CASE

BY

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This case is reported because of the unusual coincident discovery in the same patient of three different pathological conditions, syphilis, tuberculous infection, and sickle-cell anæmia.

Sickle-cell anæmia was first recognized by Herrick in 1910, and since then the disease has been extensively studied in America. The disease in its latent form—the so-called sickling trait—occurs in about 7·7 per cent. of American negroes; negroes in other parts of the world may be affected. The sickling is due to an inherent defect of the erythrocytes and behaves like a dominant Mendelian characteristic (Woofter and others, 1945). The diagnosis can only be made by demonstrating sickling of the erythrocytes, and this is readily seen in sealed preparations of fresh blood left standing for some time. The pathogenesis of sickling is not wholly understood. Sickle-cell formation is independent of external factors; *in vivo* or *in vitro* it is determined by alterations in the ratio of combined to dissociated hæmoglobin within the cell (Murphy and Shapiro, 1945). The acute phase of sickle-cell anæmia—the so-called crisis—is characterized by pyrexia, progressive anæmia, weakness, arthritic pains, myalgia, and dyspnœa.

While the latent phase may be completely asymptomatic, some clinical variants of the crisis may resemble severe shock (Tomlinson, 1945) or an acute abdominal emergency, and may end fatally. According to some authorities, the underlying pathological changes are of a thrombotic nature; the sickle-shaped erythrocytes are believed to have a special tendency to interlace and conglutinate in the small vessels, producing stasis and thrombosis. There is no specific treatment for the condition, and patients recover from a mild attack spontaneously, but sooner or later a severe relapse will end fatally. Those who survive one or more exacerbations often suffer from chronic ulcers on the legs and from scars, a fact of some importance to the venereologist who might find it difficult to distinguish these ulcers from gummatous lesions (Robinson and Tasker, 1946).

Case History

A West African coloured seaman, of good general physique, aged 34, was referred from a venereal disease clinic for admission to St. Charles' Hospital on May 24, 1947, under the care of Dr. A. H. Harkness. He was then acutely ill, complaining of general pains in the muscles and joints and of a severe cough. Pyrexia, rigors, and dyspnœa were noted. His temperature was 101·4° F., pulse 108, and respiration 22. The conjunctivæ were deeply icteric. Scars from healed ulcers were visible on both legs. The heart was normal. An impaired percussion note was elicited over the mid-zone and base of the right lung, with a pleural rub and moist crepitations. The ankle and knee jerks were absent.

The diagnosis at this stage was obscure, but further clinical and laboratory investigations brought to light the existence of a triple pathology.

Syphilis.—The patient gave a history of having contracted both syphilis and gonorrhœa in 1936, probably in America, but he could not give details of the treatment employed. In 1944, however, antisyphilitic treatment was initiated in London on account of positive serum reactions, but after the first few injections of arsenic and bismuth he defaulted. In May, 1947, he attended a venereal diseases clinic again, complaining of joint pains and headache of seven days' duration. Neurosyphilis was suspected, and an examination of the central nervous system showed absence of the abdominal reflex on the right side and of the ankle and patellar reflexes on both sides. The blood Wassermann reaction was negative but the cerebrospinal fluid contained increased globulin and showed a paretic Lange curve, with a positive Wassermann reaction.

The administration of 4·5 mega units of penicillin between April 14 and 25, 1947, was not followed by any beneficial effects. The patient's condition deteriorated rapidly, and he was admitted to St. Charles' Hospital for investigation. Re-examination of the central nervous system confirmed the absence of the ankle and patellar reflexes on both sides. The pupils were normal. The Wassermann reaction of the blood serum was negative but the Kahn test was positive., A lumbar puncture performed on June 2 yielded a normal spinal fluid with a Lange curve of 0111000000. There was no change in the above findings throughout the illness.

Tuberculosis.—The family history showed that the father died of pulmonary tuberculosis. The patient

himself had never had any other illness in the past except for the double venereal infection in 1936, already mentioned. In May 1947, he complained of loss of weight, cough, spitting of blood, and night sweats. His temperature was found to attain a nocturnal peak of 104° F. On admission the chest condition was suggestive of pulmonary tuberculosis, but repeated examination of the sputum failed to detect the tubercle bacillus. A preliminary *x*-ray examination of the chest showed extensive hilar and paratracheal adenopathy. Further *x*-ray examination demonstrated also patches of consolidation in the right upper and middle lobes. The erythrocyte sedimentation rate was 60 millimetres in 1 hour. The leucocyte count was 4,600 per cubic millimetre, of which 75 per cent. were polymorphonuclear leucocytes.

From May 27 until his death on June 19 the temperature never fell to normal level but ranged between 101° and 104° F. He continued to bring up large quantities of frothy blood-stained sputum, and auscultation of the lungs detected crepitations throughout both bases. On June 2 abdominal symptoms appeared for the first time. He complained of diffuse abdominal pain, constipation, and gaseous distention. Ascites was not present, and the liver and spleen could not be palpated. As the illness progressed the distention became worse and some free fluid appeared in the peritoneal cavity. It was obvious that peritonitis was present, but its tuberculous nature was not suspected; it was attributed to his cachectic condition and particularly to thrombotic phenomena in the veins of the portal circulation in connexion with the sickle-cell anæmia described below.

Sickle-cell Anæmia.—There was no history of previous anæmia. The first routine blood count, performed for diagnostic purposes, displayed a sickle-cell appearance in the majority of the erythrocytes. Preparations of fresh blood, kept under a cover-slip for several hours, showed an obvious sickling trait affecting as many as 90 per cent. of the erythrocytes. The sicklæmia was accompanied by progressive anæmia (see Table). The scleræ remained icteric. The urine contained a trace of albumin but no bile pigments. On June 2, two pints of carefully cross-matched blood were transfused to the patient. The response was poor as shown by the blood-count made on June 3 (see Table). The patient felt worse after the blood transfusion and two days later passed urine of a "port wine" appearance. It contained a heavy cloud of albumin, hyaline and granular casts, epithelial cells, and many erythrocytes. Spectroscopic examination showed the absorption bands of methæmoglobin. The blood urea amounted to 45 mg. per 100 millilitres. The Van den Bergh reaction was as follows:

Direct reaction	.. .. delayed 25 minutes
Indirect reaction	.. .. 4 units of bilirubin
Icteric index	 20
Thymol turbidity	.. 6 units (normal 0–4 units)
Takata Ara reaction	.. Strong positive + + +

The urine had no free bile or excess of urobilin, but urobilinogen and bile salts were in appreciable excess. In view of the unfavourable response to blood transfusion, the patient's blood was investigated as to cell fragility and abnormal agglutinins. The findings were:

TABLE

THE PATIENT'S BLOOD COUNTS

Date	Erythrocytes	Hæmoglobin %	Colour index	Leucocytes
1947 May 27	3,000,000	67	1·1	5,000
June 2	2,770,000	43	0·8	4,600
June 3	2,760,000	52	0·98	

Fragility in NaCl dilutions 0·45% NaCl no hæmolysis
Fragility in NaCl dilutions 0·40% NaCl 5% of erythrocytes hæmolysed
Fragility in NaCl dilutions 0·35% NaCl 40% of erythrocytes hæmolysed
Fragility in NaCl dilutions 0·30% NaCl 70% of erythrocytes hæmolysed
Fragility in NaCl dilutions 0·25% NaCl 100% of erythrocytes hæmolysed

Fragility decreased.

The patient's cells belonged to group A_1 and were Rh-positive; genotype R_1r, or R_1Ro. No anti-Rh or other atypical agglutinins were found in his serum, and the Coomb's test did not reveal the presence of any Rh-antibodies. The Donath-Landsteiner reaction was negative, and no other hæmolysins were demonstrable. Weak cold agglutinins were found to certain Group O and A_1 cells and also to the patient's own cells: these were not powerful enough to warrant further investigations.

The progress of the disease was not influenced in any degree by therapeutic measures. Sulphonamides and penicillin in full doses were tried, and fresh liver and sodium pentide were also given. In view of the deterioration which followed blood transfusion, it was not repeated. Death occurred on June 19, 1947; a state of severe mental confusion which passed into coma preceded the fatal outcome.

Post-mortem Findings.—A post-mortem examination was carried out on June 26. The lungs were œdematous and congested; a granulomatous tubercular focus 0·4 cm. in diameter was present at each apex. The heart showed anæmia of the myocardium. The peritoneum was affected by tuberculous peritonitis, with a greenish turbid effusion of several pints; numerous scattered caseous tubercles were seen around the diaphragm. Caseous glands up to 4·3 cm. in diameter were found above the left hilum and the bifurcation of the trachea. The para-aortic glands and those in the region of the coeliac axis and the tail of the pancreas were also caseous. The spleen measured 18 × 13 × 7 cm. The pulp was wet and of a rich dark red colour. Caseous foci up to 1·5 cm. in diameter were present. The liver showed œdema

and reticular fibrosis. The kidneys did not show pathological changes. The testes were affected by slight brown atrophy.

Comment

The interest of this case lies in the association of three different pathological states. It is obvious that death was due ultimately to tuberculous infection. Its course, severity, and spread are explained by racial predisposition. The presence of sicklæmia was probably a determining factor in the production of severe anæmia, although tuberculous toxæmia must have played an important part. The co-existence of syphilis and sickle-cell anæmia has been described in the literature, and Zimmerman and Barnett (1944) have seen the Wassermann and Kahn reactions become positive in the course of hæmolytic crisis.

Summary

A case of acute tuberculous infection, neurosyphilis, and sickle-cell anæmia is described. It presented, for obvious reasons, difficulties in diagnosis. The association is considered to be a coincidence.

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